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Portable thermographic screening for detection of acute Wallenberg's syndrome

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TITLE:

Portable Thermographic Screening for Detection of Acute Wallenberg's Syndrome

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KEYWORDS:

Thermography, body surface temperature, Wallenberg's syndrome, lateral medullary syndrome, Horner's syndrome, brainstem infarction, autonomic nervous system disorders, autonomic disturbance

SUMMARY:

Acute Wallenberg's syndrome can be misdiagnosed as a non-stroke disease, such as auditory vertigo. Thus, careful neurological examination, which is sometimes difficult for non-neurologists, is necessary for precise diagnosis. Here, we present a simple, rapid, noninvasive, and cost-effective method for detection of acute Wallenberg's syndrome using portable thermography.

ABSTRACT:

Wallenberg's syndrome (WS) is a type of brainstem infarction. WS patients often show Horner's syndrome, dissociated sensory disturbance, truncal ataxia, and hoarseness. However, they rarely show tactile sensory disturbance and paralysis of the extremities. Additionally, acute brainstem infarction is often not apparent in magnetic resonance images. These symptomatic and imaging characteristics sometimes lead to misdiagnosis of WS as a non-stroke disease, including auditory vertigo. Although careful neurological examination is necessary to prevent misdiagnosis of WS, this type of examination may be difficult for non-neurologists to whom affected patients initially present. Lateral differences in body surface temperature (BST) constitute a recognized and widespread symptom of WS. We previously reported that most acute WS patients exhibit lateral differences in BST at multiple locations and that these lateral differences in BST could easily be detected by thermographic measurement. Here, we present the method for use of portable thermography to detect acute WS, using a simple, rapid, noninvasive, and cost-effective approach. To assess lateral differences in BST among patients with suspected WS, BST was measured as soon as possible in the examination room or in the patient's bedroom.

Measurements were performed bilaterally at four locations where images could easily be acquired (face, palm of the hand, abdomen, and dorsum of the foot) using a portable thermal camera. When lateral differences in BST are observed macroscopically, especially in multiple locations on the same side, a diagnosis of WS should be suspected. Macroscopic assessment of BST laterality can be made within 2 min of the acquisition of thermographic images. This method may be useful in preventing misdiagnosis of acute WS as a non-stroke disease, especially when such patients initially present to non-neurologists.

INTRODUCTION:

Wallenberg's syndrome (WS) is a type of brainstem infarction. Acute WS patients are sometimes initially misdiagnosed with non-stroke diseases because of the symptomatic and magnetic resonance imaging (MRI) characteristics of WS. To accurately diagnose acute WS, careful neurological examination is necessary, which may be difficult for non-neurologists to whom affected patients initially present. Here, we present a simple, rapid, noninvasive, and cost-effective method for the detection of acute WS using portable thermography.

WS is caused by the infarction of a wedge of the dorsal lateral medulla oblongata, due to occlusion of the vertebral artery or posterior inferior cerebellar artery[1,2]. WS may be misdiagnosed as a non-stroke disease because of a combination of unique symptomatic and MRI characteristics that contrast with those typically observed in cerebral infarction. Hemiparesis and tactile sensory disturbance, which tend to be observed in patients with other types of cerebral infarction, are rare in WS patients; however, they exhibit various combinations of clinical symptoms, including hoarseness and dysphagia, dissociated sensory disturbance, vertigo, gaze-induced nystagmus, ataxia, and Horner's syndrome[1-7]. Another unique characteristic of WS patients is the limited severity of symptoms, which is similar to that in other types of brainstem infarctions[7-11]. Some patients with brainstem infarctions have arrived at the outpatient clinic on foot and reported only minor complaints[7]. In some patients with WS, vertigo is the only presenting symptom, and it can therefore be difficult to differentiate between WS and auditory vertigo[12]. Furthermore, WS can affect young patients, due to its potential etiology of artery dissection[2]. MRI analysis of brainstem infarction, including WS, is unique in that the high-intensity diffusion-weighted imaging signal may be delayed in some patients[7,13,14].

The above characteristics are thought to cause misdiagnosis of WS. Dysphagia may cause aspiration pneumonia or asphyxia, and artery dissection may cause subarachnoid hemorrhage[15]; therefore, overlooking WS may result in the development of life-threatening conditions for the patient. Although careful neurological examination is necessary to prevent the misdiagnosis of WS, it is likely that a patient will first present to a non-neurologist. Therefore, a rapid and simple method for screening of acute WS may be clinically useful.

Previously, we reported that 89% of acute WS patients exhibit laterality of BST, which is presumed to result from disturbance of the central autonomic nervous tract due to infarction at the lateral medulla[7]. Because this autonomic nervous tract descends from the lateral brainstem (including the ventro-lateral medulla) and contains the connective pathway of sweating and skin blood flow[16], disturbance of sweating and vasoconstriction lead to increased BST on the

ipsilateral side of WS. In the prior report, we also showed that the laterality of BST can be easily detected within 2 min using thermographic measurement in most patients with WS[7,17]. Here, we report a method for the detection of laterality of BST using thermography, which may be useful in preventing misdiagnosis of acute WS.

PROTOCOL:

All methods described here were approved by the Human Research Ethics Committee Institutional Review Board of Kanto Central Hospital.

NOTE: We used a commercially available portable thermal camera and dedicated software (see the **Table of Materials**), and have constructed our protocols based on the use of these specific instruments.

1. Preparation for measurements

1.1. Charge the thermal camera before use.

1.2. Turn on the camera.

1.3. Push the center button on the camera to display the menu. Select **Color** from the menu and select **Iron** or **Rainbow** color.

1.4. Push the center button on the camera to display the menu. Select **Measurement** and then **Center spot measurement** to measure the BST in real time.

2. Patient selection

2.1. Test all patients with suspected WS. Patients with dizziness, vertigo, ptosis, hoarseness, dysphagia, anisocoria, or dissociated sensory disturbance may have WS.

2.2. Subjectively determine the laterality of BST by palpating the patient with suspected WS.

3. Acquisition of thermographic images

3.1. Instruct the patient to take off their socks and shoes. Have the patient remove clothing (if consent is granted) to enable examination of the abdominal region.

3.2. Acquire images in an examination room or in the patient's bedroom, as soon as WS is suspected. Ask the patient to assume a supine posture or sitting position during image acquisition. Ask the photographer to stand 50–100 cm from the patient.

NOTE: Lighting conditions in the room do not influence the results of the thermographic measurements.

3.3. Acquire one image at each of four areas for each patient: 1) frontal face, 2) bilateral palm, 3) abdomen, and 4) bilateral dorsum of the foot (**Figure 1**). These four areas are uncomplicated locations for image acquisition, even in bedridden patients who cannot move because of dizziness, vertigo, nausea and vomiting.

NOTE: Blankets or drafts caused by air conditioning may influence the BST. If such influence is suspected, cover all extremities and the trunk with blankets, then acquire additional images after an interval of >10 min. Drip infusion therapy at the extremities also may influence the BST. If possible, slow down or stop the infusion, then acquire images after an interval of >10 min.

4. Assessing the laterality of BST

4.1. Consider BST to exhibit laterality when the BST between the right and left sides is markedly different macroscopically and the degree of laterality is >0.5 °C[18]. If the laterality of BST is not obvious or appears to be ≤0.5 °C, perform advanced analysis with dedicated software as described below.

NOTE: When laterality of BST is observed in multiple locations on the same side of the patient, there is a strong possibility that the patient has WS in the ipsilateral side of the medulla on the warmer side, as determined by BST.

5. Advanced assessment of the laterality of BST

5.1. Initialize the thermal imaging and analysis software.

5.2. Select and open the acquired image to be analyzed.

5.3. Select the **Ellipse** measurement button on the left side tab, and indicate ellipses with diameters of >5 mm at four locations: 1) the nasolabial fold on the face; 2) the palm of the hand; 3) thoracic spine levels 8–10, approximately 5 cm from the umbilicus of the torso; and 4) the center of the dorsum of the foot.

5.4. Check the average BST from each location and compare it to the BST on the contralateral side of the body.

6. Confirming WS

6.1. Perform a careful neurological examination if the patient exhibits laterality of BST to confirm a diagnosis of WS. In addition to screening by neurological examination, check for the presence of Horner's syndrome including ptosis and constricted pupil, as well as the presence of dissociated sensory disturbance, to determine whether the patient exhibits acute WS.

6.2. Consider hospital admission when WS cannot be ruled out based on the results of thermographic measurement and neurological examination.

6.3. Consider repeated thin-slice brainstem MRI after an interval of a few days to diagnose WS.

REPRESENTATIVE RESULTS:

Acquisition of thermographic images and macroscopic assessment to determine whether BST exhibits laterality may be performed within 2 min in most patients. Most acute WS patients exhibit laterality of BST at multiple locations. Some patients exhibit laterality of BST throughout the body (**Figure 2A**), whereas some exhibit laterality only in a few locations (**Figure 2B**). The warmer side, as determined by BST, is ipsilateral to the location of WS (**Figure 2D,E**). Importantly, however, a WS patient with a very small infarction may not exhibit laterality of BST (**Figure 2C,F**). When a patient does not exhibit a central nervous disorder (e.g., auditory vertigo), laterality of BST is typically not observed **(Figure 1**). However, when a patient exhibits vascular stenosis, BST may be lower in the extremities with vascular stenosis than in extremities on the contralateral side. Laterality of BST is observed in only one limb in nearly all patients with vascular stenosis. However, patients may exhibit vascular stenosis in both the upper and lower limbs (**Figure 3**).

The precise degree of BST can be analyzed with dedicated software (**Figure 4**). This analysis may be required when the laterality of BST is not apparent macroscopically, especially on the face and trunk, because lateral differences in the faces and trunks of WS patients tend to be smaller than those of the extremities in such patients[7].

FIGURE AND TABLE LEGENDS:

Figure 1: Thermographic images of the face, bilateral palm, abdomen, and bilateral foot of a patient with auditory vertigo. Laterality of BST is not detected. The patient's face is blurred to protect privacy.

Figure 2: Thermographic images and MRI findings of WS patients. (**A, D**) WS patient with laterality of BST throughout the body. The warmer side of the patient's body is ipsilateral to the infarction. (**B, E**) WS patient with laterality of BST of the upper and lower limbs. The warmer side is also ipsilateral to the infarction. (**C, F**) Brain MRI/diffusion-weighted imaging of this patient revealed a very small high-intensity lesion at the edge of the lateral medulla, but no lateral difference in BST. Patients' faces are blurred to protect privacy. **Figure 2B–F** were modified from Takahashi et al.[7].

Figure 3: Left upper and right lower extremities of a patient with arterial sclerosis and vascular stenosis. Arterial sclerosis and vascular sclerosis diagnoses were based on ankle-brachial index; thermography reveals higher BST on the contralateral side.

Figure 4: Laterality of BST in the abdomen of a WS patient. Results were equivocal macroscopically, but analysis by ellipse measurement in the analysis software showed a 0.6 °C discrepancy in the average BST between the right and left sides of the abdomen.

DISCUSSION:

Critical steps of this protocol are the establishment the initial suspicion of WS and the decision to acquire thermographic images of the patient. Acquiring thermographic images and assessing the laterality of BST is a simple approach, even for non-neurologists who may examine patients upon initial presentation to the emergency department or a general clinic. If a patient exhibits laterality of BST, especially at multiple locations on the same side, the physician should consider the possibility of WS. Because most WS patients with laterality of BST also exhibit other clinical symptoms, including Horner's syndrome and dissociated sensory disturbance[7], the physician should then perform a careful neurological examination or consult a neurologist. This protocol may reduce the possibility of overlooking WS.

A limitation of this method is that it cannot be used to confirm a diagnosis of WS—it should only be used when WS is suspected. To confirm a diagnosis of WS, neurological examination and MRI are needed. However, if WS is suspected by a primary physician, this protocol reduces the possibility that the patient will be allowed to go home, thereby reducing the likelihood of misdiagnosis of WS. Other central nervous diseases can result in laterality of BST[6]; these include other types of brainstem infarctions, as well as supratentorial brain infarction, which may impair the autonomic nervous tract. However, these diseases can be diagnosed easily without thermography because of the high prevalence of hemiparesis and tactile sensory disturbance that are readily observed by physicians who evaluate such patients at the time of initial presentation. Vascular stenosis of the extremities can also result in the laterality of BST[19]. When a patient exhibits >19% laterality on branch-ankle pulse wave velocity[20], the patient may have vascular stenosis, which can affect BST. To rule out these diseases other than WS and to confirm the diagnosis of WS, repeated brain MRI[7,13,14], ankle-brachial index[20], and contrast enhancement computed tomography are sometimes necessary.

Another limitation is that the characteristics of the thermal camera we used do not fulfill the equipment recommendation of the thermography guidelines from the International Academy of Clinical Thermography[21]. However, the thermography characteristic assessed in this study was the ability to distinguish the laterality of BST by >0.5 °C. Because the camera can distinguish differences in BST of ≥0.1 °C, the characteristics of our camera may not influence the results of this method.

The degree of lateral discrepancy of BST in most WS patients is greatest at the foot region[7]; thus, manual assessment of the laterality of BST by palpation of the lower extremities may be an alternative method to this protocol when thermography cannot be used. However, thermographic measurement is superior to palpation because thermographic measurement offers greater objectivity.

The most important merits of this method are that thermographic measurement is rapid, simple, noninvasive, and cost-effective. Although the sensitivity and specificity of this method for identifying WS and other diseases, including other central nervous diseases and auditory vertigo, have not yet been proven, thermographic measurement could be used as a triage method for clinicians during evaluation of patients with dizziness or vertigo. Multicenter studies regarding

the laterality of BST are warranted for patients with WS, as well as for those with other central nervous diseases or dizziness.

ACKNOWLEDGMENTS:

Not applicable

DISCLOSURES:

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Figure

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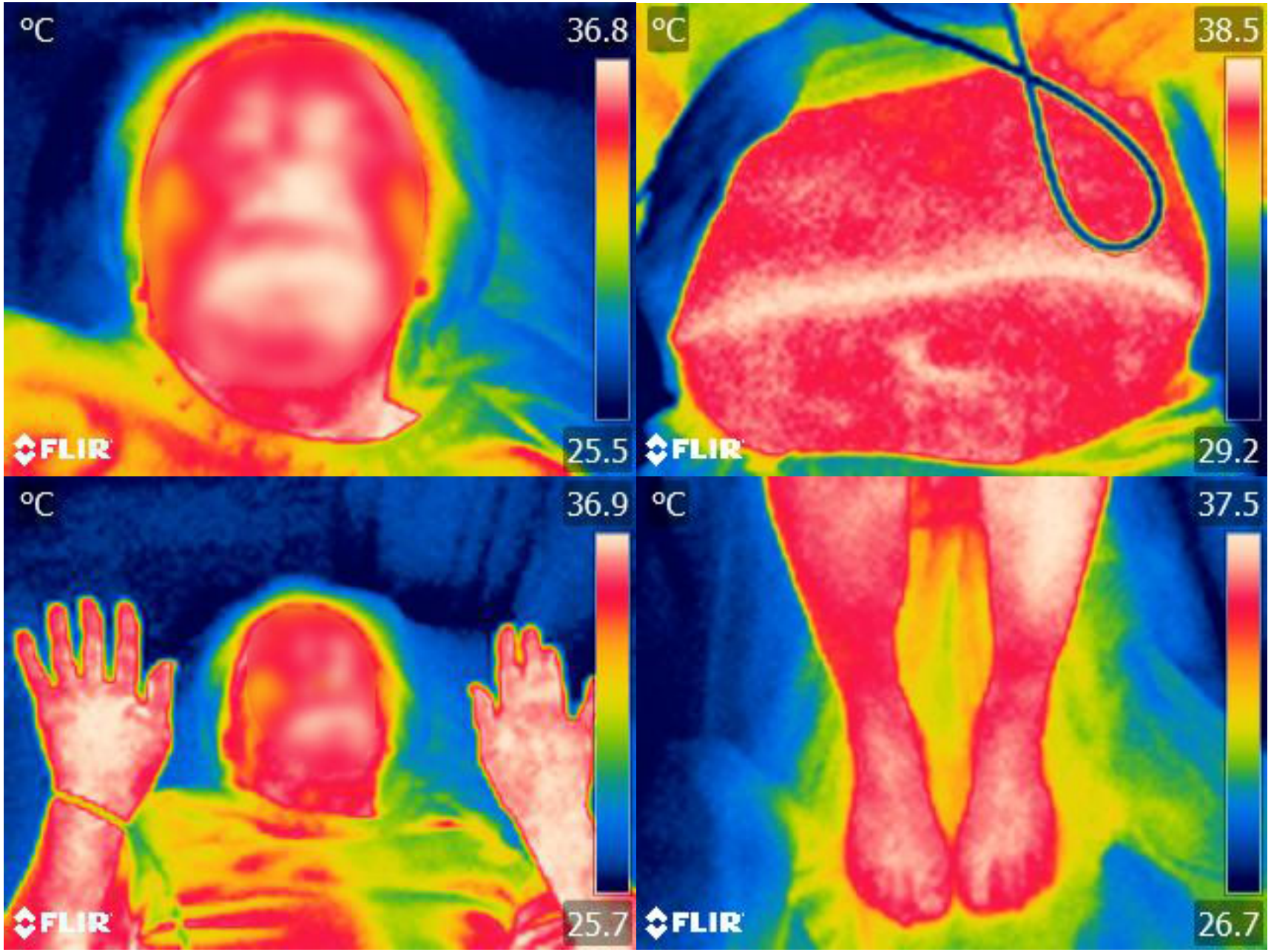
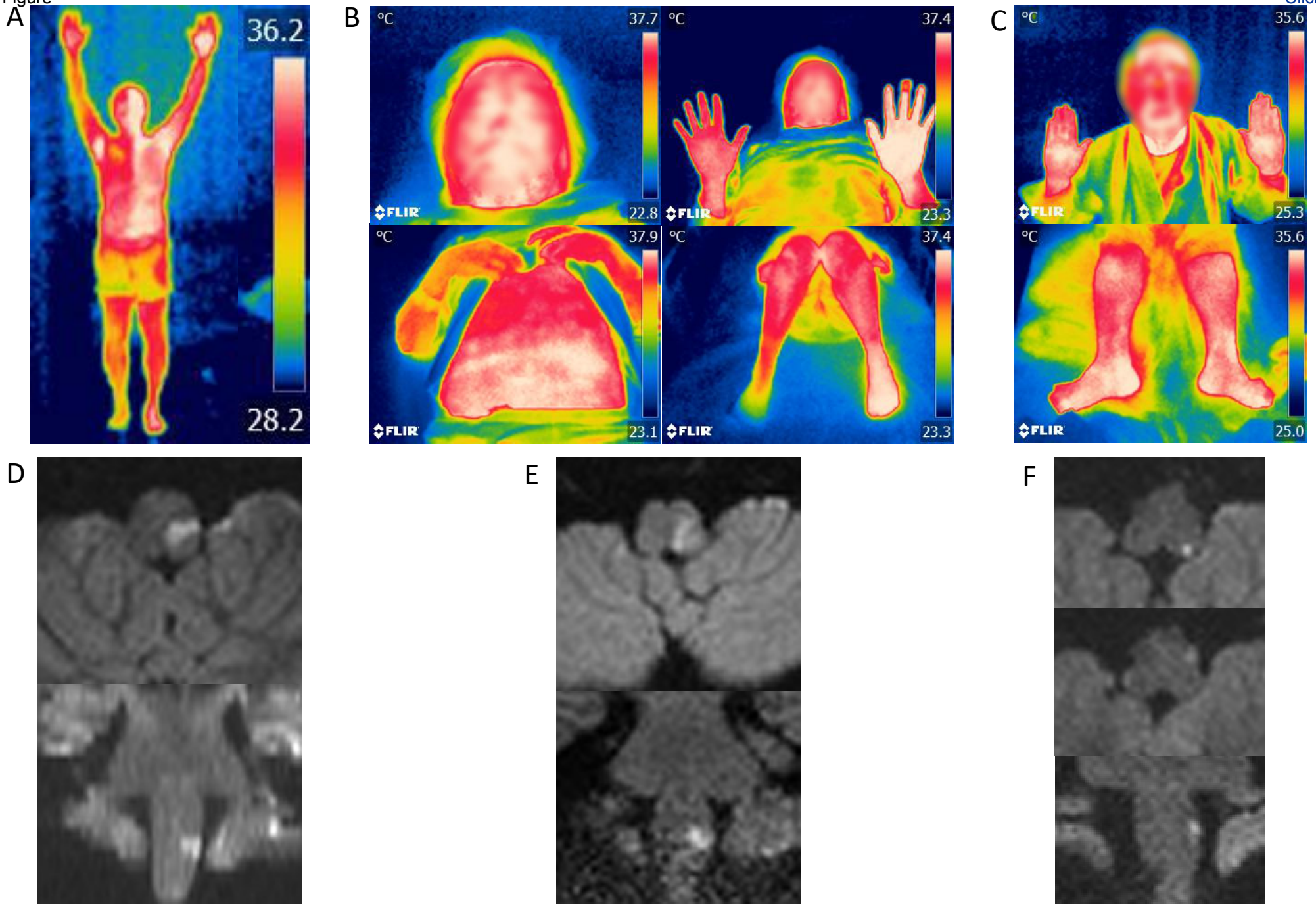


Figure 1

Figure



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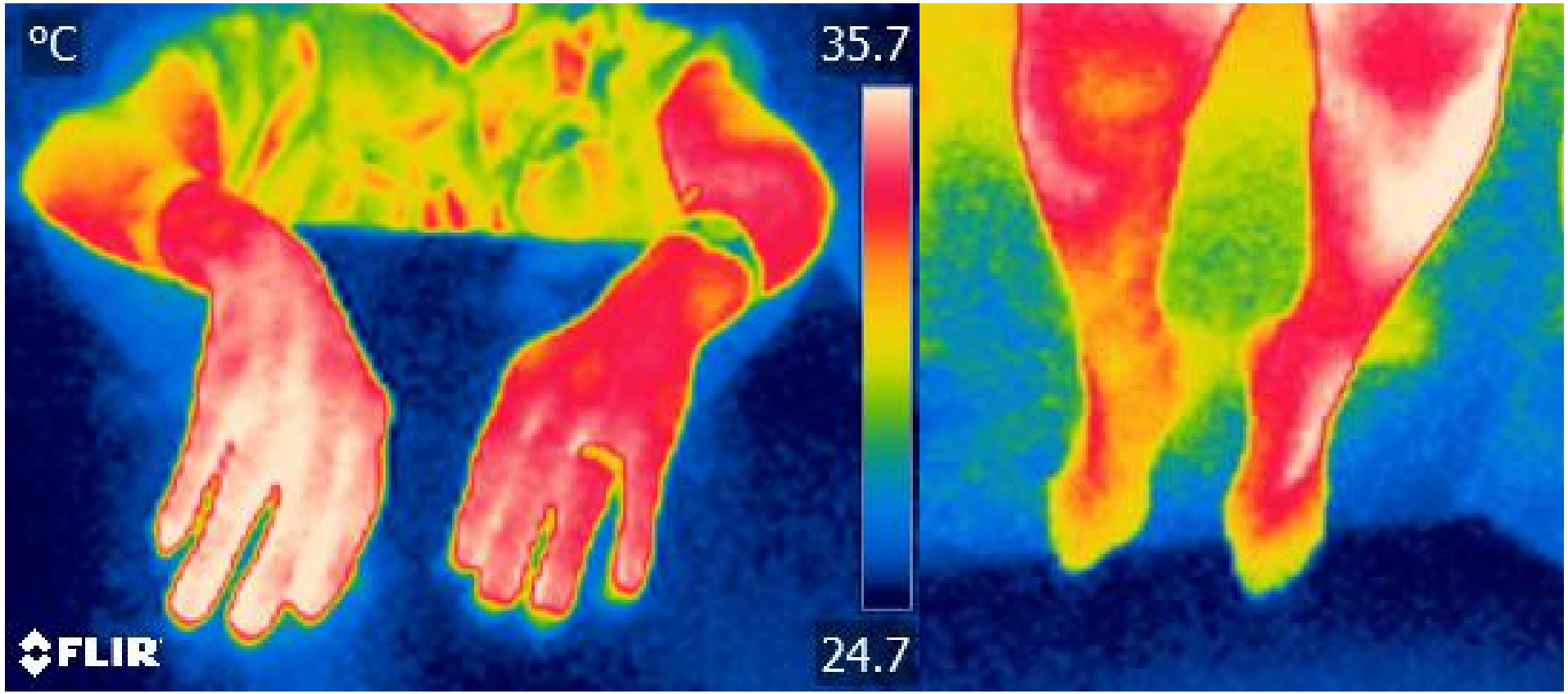

Figure 3

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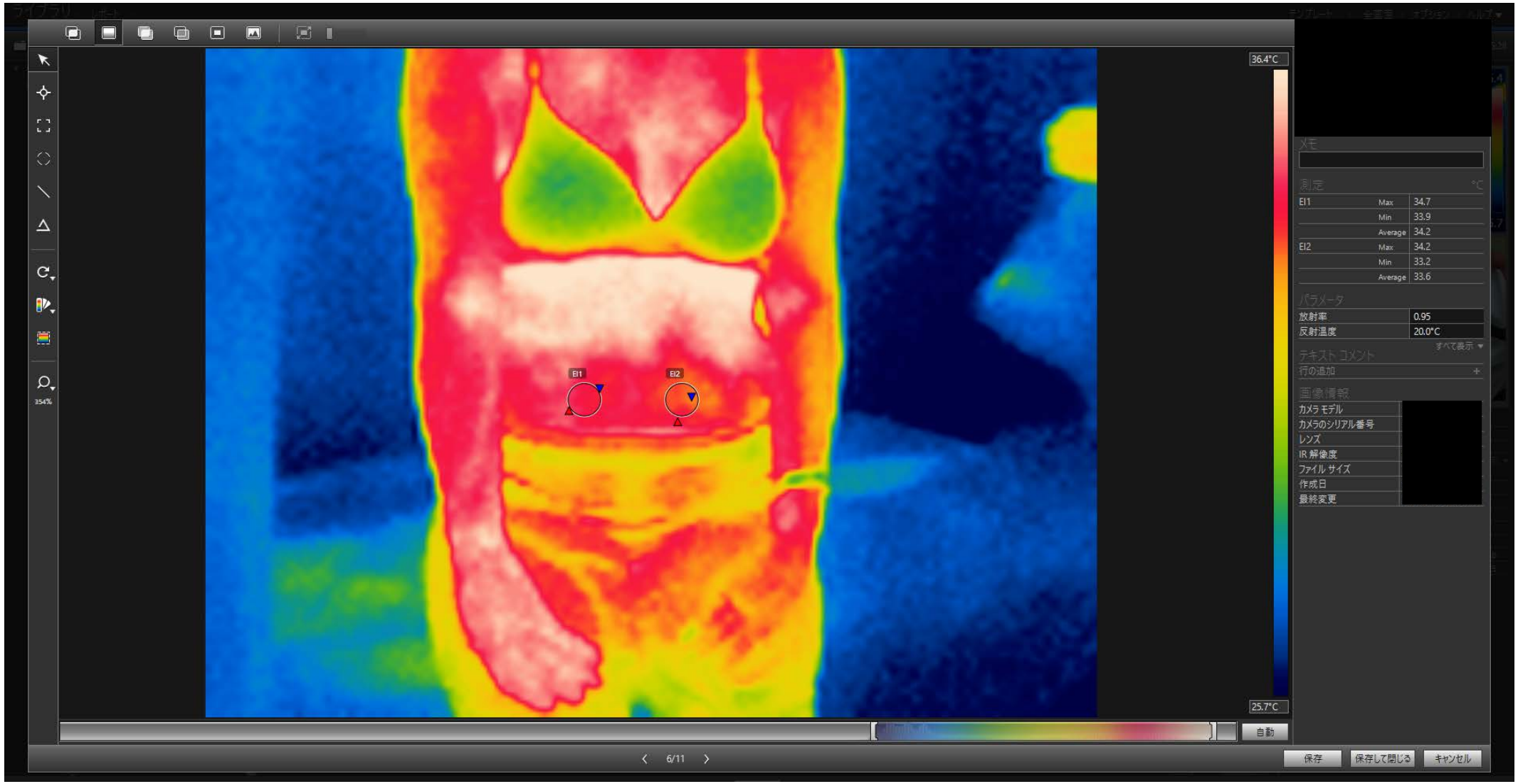

Figure 4

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Institution:	Kanto Central Hospital
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Signature:	Makoto Takahashi
Date:	October, 31, 2018

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June 25, 2019

Dr. Alisha DSouza
Senior Review Editor
JoVE: Journal of Visualized Experiments

Dear Dr. DSouza:

Thank you very much for reviewing our manuscript entitled, "**Thermographic measurements of laterality of body surface temperature to prevent misdiagnosis of acute Wallenberg's syndrome.**"

In the following pages, we have replied to your inquiries and those of the three reviewers. We believe that the manuscript has been greatly improved by revisions in this review process, and we hope that our explanations and revisions are satisfactory for publication in *JoVE: Journal of Visualized Experiments*. For your convenience, we added line numbers in the left margin in the text.

We are hereby resubmitting our manuscript, with the revised title of "**Portable thermographic screening for detection of acute Wallenberg's syndrome**," along with four figures and one table of materials. We wish to thank you again for allowing us a chance to rewrite our manuscript, and we look forward to your response regarding further review of our manuscript.

Sincerely,

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General responses to the Editor and the three reviewers

Thank you very much for your meticulous review of our manuscript. We have checked all comments and agree with these critiques. We have responded to the comments and incorporated the corresponding revisions in the accompanying manuscript.

Thank you,
Makoto Takahashi, MD, PhD.
(*Corresponding author*)

Reply to Editor

We thank the editor for these comments, which we have considered when revising our paper.

1. The author should proofread the manuscript to avoid spelling or grammar error.
   - We previously received English proofreading by *Editage*®, and have asked the company to perform further proofreading for the revised manuscript.
2. The author should obtain explicit copyright permission.
   - We thank the editor for this important comment. Our prior report is open access and copyright permission is provided under a creative commons license.
3. The author should change the title
   - In accordance with the editor's comment, we changed the title to "Portable thermographic screening for detection of acute Wallenberg's syndrome."
4. The author should revise line 70-72.
   - In accordance with the editor's comment, we revised lines 70-72 (now lines 67-68) as follows: "WS is caused by the infarction of a wedge of the dorsal lateral medulla oblongata, due to occlusion of the vertebral artery or posterior inferior cerebellar artery[1,2]."
5. The author should revise the protocol.
   - In accordance with the editor's comment, we revised the protocol.
6. Move lines 146-157 to the discussion.
   - In accordance with the editor's comment, we moved lines 146-157 to the Discussion (now lines 233-243).
7. Add more detail the protocol step.
   - As we noted above, we have revised the protocol in accordance with the editor's comment.
8. The author should explain how to turn on center spot measurement.
   - In accordance with the editor's comment, we revised the protocol in lines 113-114.
9. The author should explain the position of patients.
   - In accordance with the editor's comment, we have described the patient's position in line 129-131.
10. How many pictures should be taken?
    - We thank the editor for this important question. We consider one image to be necessary for each part, and we have written that in the protocol section (line 133).
11. How about light condition?
    - In accordance with the editor's comment, we described the lighting conditions in lines 130-131.

12. The author should explain how to use the software
    - In accordance with the editor’s comment, we revised the protocol in lines 157-169.
13. The author should explain how to perform a careful neurological exam.
    - In accordance with the editor’s comment, we described the method for performing a careful neurological exam in the protocol section (lines 173-176).

Reply to Reviewer #1

We thank the reviewer for these comments and useful suggestions, which have helped us to improve our paper. As indicated in the responses that follow, we have considered all of these comments and suggestions when revising our paper.

Major concerns

1. There is a problem about the similarity between this paper and the prior paper.
    - In accordance with the reviewer's comment, we rewrote a large portion of text throughout the body of the manuscript.
2. The author should explain the precise mechanism of laterality of BST.
    - In accordance with the reviewer's comment, we have explained the mechanism of laterality of BST in lines 90-93, along with a new reference (reference No. 16).
3. The sample size is too small.
    - We thank the reviewer for this important comment. Wallenberg's syndrome is relatively rare among cerebral infarctions, and we could therefore only include nine patients in this manuscript. We are currently collecting data from additional patients with complaints of dizziness and preparing these data for submission as a new report.

Reply to Reviewer #2

We thank the reviewer for this comment, which has helped us to improve our paper.

Major concerns

1. Circumstances for taking thermographic pictures is very important.
    - In accordance with the reviewer's comment, we have described what circumstances could influence the BST and have explained how to avoid these effects (lines 138-143).

Reply to Reviewer #3

We thank the reviewer for these comments and useful suggestions, which have helped us to improve our paper. As indicated in the responses that follow, we have considered all of these comments and suggestions when revising our paper.

Manuscript summary

1. The author should give more objective focus on the WS in introduction.
    - In accordance with the reviewer's comment, we have rewritten the Summary and the Introduction to clearly convey the objective focus on WS in this study.

Major concerns

2. The author should make clear the usefulness of using thermography for detecting WS clinically.
    - In accordance with the reviewer's comment, and to emphasize the usefulness of thermography for clinical detection of WS, we have rewritten the summary and the Introduction.

Minor concerns

3. Could other disease except WS change the body temperature?
    - We thank the reviewer for this important question. Indeed, BST can exhibit laterality in other types of brainstem infarctions and in supratentorial infarction. We agree that our description may have been confusing, which led to the inference that the laterality of BST is specific to WS. In this report, we aimed to emphasize the high frequency of misdiagnosis of acute WS, as well as the high frequency of laterality of BST in acute WS; thus, we did not assess the specificity of laterality of BST in WS. We have described these as limitations in the Discussion section (lines 232-245).
4. Spell out the acronym MRI.
    - In accordance with the reviewer's comment, we spelled out the acronym "MRI" in line 63.
5. The author apparent the reason that these places were selected to take pictures.
    - We appreciate this important comment. Many patients with dizziness or vertigo could not sit, stand, or move because of nausea or vomiting. These four places were therefore uncomplicated locations for thermographic images, even for bedridden patients. We have added this explanation in lines 52-54 and lines 134-136.
6. A better explanation of the technique used for image acquisition is required.
    - In accordance with the reviewer's comment, we changed the protocol section to provide greater detail regarding image acquisition (lines 123-143).

7. The author should explain better the mean of laterality, and should consider the temperature difference in normal individuals.
    - We thank the reviewer for this valuable comment. The report that the reviewer mentioned described abnormal lateral differences of BST in regional view; thus, we set the abnormal degree of lateral difference of BST as > 0.5°C. We also added that report as a reference in the revised manuscript.
8. The author should describe ROIS better.
    - In accordance with the reviewer's comment, we described the diameter of the ROI in lines 163-164.
9. The author should clear what is most important findings in representative results.
    - We appreciate this important suggestion. We aimed to show four important points regarding thermographic results. First, WS patients could show some degree of laterality of BST, as indicated in Figs. 2A, 2B, 2D, and 2E. Second, a small number of WS patients with small infarctions may not show laterality of BST, as indicated in Figs. 2C and 2F. Third, non-central nervous disease patients typically do not show laterality of BST, as indicated in Fig. 1. However, patients with vascular stenosis should be closely monitored for laterality of BST, as indicated in Fig. 3. Finally, analysis of BST with dedicated software could clarify the laterality of BST, particularly when this laterality is not apparent macroscopically.
    - To clarify these points, we have rewritten the text in the Representative Results section (lines 184-198).
10. The author should clear the reference about checking the temperature with hands.
    - We changed the text regarding comparison of thermography and palpation in the main text (lines 252-256), because we could not find references that appropriately addressed this comment.
11. The author should clear the reason that FLIR E5 was chosen for this research. Has any previous study been done using this camera?
    - We thank the reviewer for this important comment. As the reviewer noted, thermography guidelines recommend higher functional thermography than the FLIR E5 to promote validity and quality imaging (http://www.iact-org.org/professionals/thermog-guidelines.html). However, these instruments are expensive for general clinical hospitals.
    - The main theme of this study was to establish a simple, rapid, noninvasive, and cost-effective method to prevent misdiagnosis of WS.
    - In addition, the thermography characteristic assessed in this study was the ability to distinguish the laterality of BST by > 0.5°C.

- The FLIR-E5 is comparatively less expensive than thermography for human clinical research and can distinguish differences in BST of ≥ 0.1°C.
- There have been some reports regarding measurement of body temperature with the FLIR-i series, which has characteristics inferior to those of the FLIR E5 (Int J Biometeorol (2017)61:2119-2125, Ostomy Wound Management (2012)58:20-31).
- Recently, a more cost-effective cell phone attached inflamed camera (FLIR ONE), with characteristics also inferior to those of FLIR E5, has been used for clinical studies (Ann Plast Surg (2018)80:S236-238, Burns (2017)43:1516-1523).
- To clarify these reasons for use of the FLIR E5, we added new limitations in the Discussion (lines 246-251).